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- (71) Applicant: BRACCO RESEARCH SA [—/CH]; 31, route de la Galaise, CH-1228 Plan les Ouates (CH).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): SCHNEIDER, Michel [FR/-]; 34, Route d'Annecy, CH-1256 Troinex (CH). BUSSAT, Philippe [FR/FR]; 46, Allée du Salève, F-74160 Feigères (FR). YAN, Feng [FR/CH]; 7, Chemin des Champs Gottreux, CH-1216 Grand Lancy (CH). GUILLOT, Christian [FR/FR]; 70, Chemin de Zone, F-74160 Beaumont (FR).
- (74) Agent: RAVIZZA, Claudio; Bracco Research SA, Intellectual Property Department, 31, route de la Galaise, CH-1228 Plan les Ouates (CH).
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- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
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(54) Title: ULTRASOUND CONTRAST AGENTS AND PROCESS FOR THE PREPARATION THEREOF

(57) Abstract: Method for preparing a lyophilized matrix and, upon reconstitution of the same, a respective injectable contrast agent comprising a liquid aqueous suspension of gas-filled microbubbles stabilized predominantly by a phospholipid. The method comprises preparing an emulsion from an aqueous medium, a phospholipid and a water immiscible organic solvent. The emulsion is then freeze-dried and subsequently reconstituted in an aqueous suspension of gas-filled microbubbles. The method allows to obtain suspensions comprising microbubbles having a relatively small diameter and a narrow size distribution.





A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K49/22 A61K49/18 A61K9/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

 $\begin{array}{ll} \mbox{Minimum documentation searched (classification system followed by classification symbols)} \\ \mbox{IPC 7} & \mbox{A61K} \end{array}$

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/08716 A (MARSDEN JOHN CHRISTOPHER; OMTVEIT TORE (NO); NYCOMED IMAGING AS (NO)) 25 February 1999 (1999-02-25) page 32, line 1 - page 33, line 30	35-40
X	EP 1 228 770 A (BRACCO RES S A) 7 August 2002 (2002-08-07) page 9, line 35 - page 14, line 17	35–40
Y	page 9, Time 35 - page 14, Time 17	1-34
X	WO 98/05364 A (MARSDEN JOHN CHRISTOPHER; BRAENDEN JORUNN (NO); DUGSTAD HARALD (NO);) 12 February 1998 (1998-02-12) page 22, line 15 - page 23, line 30	35-40
X	US 6 280 705 B1 (KLEIN DAVID H ET AL) 28 August 2001 (2001-08-28) claims; examples	35–40

X Further documents are listed in the continuation of box C.	Patent family members are listed in annex.
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Date of the actual completion of the international search	Date of mailing of the international search report
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	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 146 657 A (MATSUNAGA TERRY ET AL) 14 November 2000 (2000-11-14) claims; table 5	35-40
Y	WO 96/09037 A (LIPOSOME CO INC) 28 March 1996 (1996-03-28) page 12; claims	1-34
A	WO 97/40858 A (IMARX PHARMACEUTICAL CORP) 6 November 1997 (1997-11-06) the whole document	1-40
A	SCHNEIDER M ET AL: "BR1: A NEW ULTRASONOGRAPHIC CONTRAST AGENT BASED ON SULFUR HEXAFLUORIDE-FILLED MICROBUBBLES" INVESTIGATIVE RADIOLOGY, PHILADELPHIA, PA, US, vol. 30, no. 8, 1 August 1995 (1995-08-01), pages 451-457, XP000611270 the whole document	1-40
Y	WO 99/36104 A (DU PONT PHARM CO) 22 July 1999 (1999-07-22) pages 12-19	1-34
E	EP 1 419 789 A (BRISTOL MYERS SQUIBB PHARMA CO) 19 May 2004 (2004-05-19) the whole document	1-34
X	US 2002/102217 A1 (HELLEBUST HALLDIS ET AL) 1 August 2002 (2002-08-01) example 11	,1
		`
•		

Patent document dted in search report		Publication date		Patent family member(s)	Publication date
WO 9908716	A	25-02-1999	AU EP WO JP NO ZA	8816198 A 1007103 A2 9908716 A2 2001515055 T 20000622 A 9807483 A	08-03-1999 14-06-2000 25-02-1999 18-09-2001 10-03-2000 21-05-1999
EP 1228770	Α	07-08-2002	EP	1228770 A1	07-08-2002
WO 9805364	A	12-02-1998	AU CA CN CZ EP WO IL JP JP KR NO NZ US	3780497 A 2262908 A1 1227502 A ,B 9900289 A3 0918546 A2 9805364 A2 128345 A 2000517296 T 2004002453 A 2000029780 A 990276 A 334365 A 2002106328 A1	25-02-1998 12-02-1998 01-09-1999 14-07-1999 02-06-1999 12-02-1998 24-06-2003 26-12-2000 08-01-2004 25-05-2000 22-01-1999 28-10-1999 08-08-2002
US 6280705	B1 .	28-08-2001	US US AUU AU	5798091 A 5605673 A 2002031476 A1 731671 B2 4922196 A 767705 B2 5199701 A 2212113 A1 1182373 A 0812214 A1 973496 A 9802095 A2 11501305 T 973489 A 321952 A1 9626746 A1 5720938 A 5626833 A 5695741 A 2004033199 A1 6287539 B1 2002028179 A1 6280704 B1 694135 B2 7478294 A 8933898 A 2164813 A1 0711179 A1 9501164 T 2002098151 A1 9503835 A1 5639443 A 6372195 B1 6258339 B1 2002051750 A1	25-08-1998 25-02-1997 14-03-2002 05-04-2001 18-09-1996 20-11-2003 30-08-2001 06-09-1998 17-12-1997 26-08-1997 28-01-1999 02-02-1999 27-08-1997 05-01-1998 06-09-1996 24-02-1998 06-05-1997 09-12-1997 19-02-2004 11-09-2001 07-03-2002 28-08-2001 16-07-1998 28-02-1995 14-01-1999 09-02-1995 15-05-1996 04-02-1997 25-07-2002 09-02-1995 17-06-1997 16-04-2002 10-07-2001 02-05-2002

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6280705 B1		US 2002054854 A1	09-05-2002
US 6280705 B1 US 6146657 A	14-11-2000	US 2002054854 A1 US 5773024 A US 5585112 A US 5469854 A US 5228446 A US 5088499 A US 5542935 A US 5580575 A US 6551576 B1 AT 235228 T AT 270878 T AU 1004399 A AU 2185095 A AU 708341 B2 AU 3146595 A BR 9509011 A CA 2177713 A1 CA 2200061 A1 CN 1158082 A , B DE 69432358 D1 DE 69432358 D1 DE 69432358 T2 EP 0740528 A1 EP 0788348 A1 JP 10505900 T JP 9506098 T WO 9515118 A1 WO 9608234 A1 US 6315981 B1	09-05-2002
WO 9609037 A	28-03-1996	US 5733572 A US 5922304 A US 5705187 A US 6088613 A US 5656211 A US 6461586 B1 US 6039557 A AT 233574 T AU 696056 B2 AU 6953794 A AU 683900 B2 AU 7043194 A AU 8840698 A CA 2164845 A1 CA 2164846 A1 CN 1125389 A ,B CN 1137748 A DE 69432219 D1 DE 69432219 T2 DK 712293 T3 EP 1252885 A2 EP 0802788 A1 EP 0712293 A1 WO 9609037 A1 EP 0783295 A1	31-03-1998 13-07-1999 06-01-1998 11-07-2000 12-08-1997 08-10-2002 21-03-2000 15-03-2003 27-08-1998 03-01-1995 27-11-1997 03-01-1995 04-02-1999 22-12-1994 22-12-1994 26-06-1996 11-12-1996 10-04-2003 04-12-2003 30-06-2003 30-10-2002 29-10-1997 22-05-1996
WO 9740858 A	06-11-1997	US 5776429 A AU 2451097 A	07-07-1998 19-11-1997

14			U۷		 		٠.	•	•
 п	_	11	114	.,	 	u	_	и	

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
WO 9740858 A		CN EP JP US WO	1216925 A 0923383 A1 2000510108 T 6033646 A 9740858 A1	19-05-1999 23-06-1999 08-08-2000 07-03-2000 06-11-1997
WO 9936104 A	22-07-1999	AU BR CN EA EP HR HU JP NO NZ PL WO US ZA	746067 B2 2115599 A 9907066 A 2317921 A1 1288373 T 2978 B1 200000422 A 1419789 A2 1027035 A2 990012 A1 0100206 A2 2002509121 T 20003471 A 505082 A 342473 A1 10312000 A3 9936104 A2 2001003580 A1 2004057991 A1 9900247 A	11-04-2002 02-08-1999 04-09-2001 22-07-1999 21-03-2001 26-12-2002 17-12-2001 19-05-2004 16-08-2000 31-10-1999 28-06-2001 26-03-2002 29-08-2000 26-11-2002 04-06-2001 07-11-2000 22-07-1999 14-06-2001 25-03-2004 14-07-2000
EP 1419789 A	19-05-2004	EP AUU BRACN EEP HUU NOZ PKOUS VUS VUS VUS VUS VUS VUS VUS VUS VUS V	1419789 A2 746067 B2 2115599 A 9907066 A 2317921 A1 1288373 T 2978 B1 200000422 A 1027035 A2 990012 A1 0100206 A2 2002509121 T 20003471 A 505082 A 342473 A1 10312000 A3 9936104 A2 2001003580 A1 2004057991 A1 9900247 A	19-05-2004 11-04-2002 02-08-1999 04-09-2001 22-07-1999 21-03-2001 26-12-2002 17-12-2001 16-08-2000 31-10-1999 28-06-2001 26-03-2002 29-08-2000 26-11-2002 04-06-2001 07-11-2000 22-07-1999 14-06-2001 25-03-2004 14-07-2000
US 2002102217 A1	01-08-2002	US AU AU AU AU AU AU	6331289 B1 249247 T 733477 B2 4718297 A 733495 B2 4786697 A 4786797 A 4786897 A 4786997 A	18-12-2001 15-09-2003 17-05-2001 22-05-1998 17-05-2001 22-05-1998 22-05-1998 22-05-1998 22-05-1998 22-05-1998

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
US 2002102217 A1		BG	103438 A	31-01-2000
		BG	103439 A	31-01-2000
		BR	9712683 A	19-10-1999
•		BR	9713978 A	02-05-2000
		CA	2269985 Al	07-05-1998
		CA	2270120 A1	07-05-1998
		CN	1440816 A	10-09-2003
		CN	1238700 A	15-12-1999
		CN	1234742 A	10-11-1999
		CZ	9901494 A3	15-09-1999
		DE	69724817 D1	16-10-2003
		DE	69724817 T2	01-07-2004
		EP	1007101 A2	14-06-2000
		EΡ	0973552 A2	. 26-01-2000
		· EP	0991427 A2	12-04-2000
		EP	0971747 A2	19-01-2000
·		EP	0946202 A2	06-10-1999
		EP	0963209 A2	15-12-1999
, ·		ES	2206689 T3	16-05-2004
	•	WO	9818500 A2	07-05-1998
·		WO	9818501 A2	07-05-1998
		MO	9818495 A2	07-05-1998
		MO	9818496 A2	07-05-1998
		WO	9818497 A2	07-05-1998
		WO	9818498 A2	07-05-1998
		HU	0000357 A2	28-06-2000
		JP	2001511765 T	14-08-2001
		JP	2001503407 T	13-03-2001
		JP	2002515889 T	28-05-2002
		JP	2001502719 T	27-02-2001 25-08-2000
		KR	2000052829 A	25-08-2000 25-08-2000
	,	KR	2000052830 A 991889 A	25-08-2000 28-06-1999
		NO NO	991889 A 991890 A	28-06-1999
		NO NZ	335596 A	27-10-2000
		NZ NZ	335799 A	24-11-2000
		US	6264914 B1	24-07-2001
·		US	6051207 A	18-04-2000
		US	0031207 A	10042000